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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/530,363	GABERT, JEAN	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to Applicant's response, filed on February 17, 2004. In Applicant's February 17, 2004 response, Applicant cancelled all of the previous claims and submitted new claims 43-62. Accordingly, all of the previous objections and rejections, which were directed to Claims 17-21, 24-27, 29-32 and 36-42 have been withdrawn, as they have been cancelled. This action contains new rejections necessitated by Applicant's amendments, and therefore, this action is made FINAL.

THE FOLLOWING ARE NEW GROUNDS OF OBJECTION/REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

Specification

2. Claims 43-62 are objected to because of the following informalities:

A) Claims 43-57 are objected to because Claim 43 recites, "An in vitro diagnostic method for detecting translocation of DNA sequence", which could be amended to recite, "An in vitro diagnostic method for detecting **a** translocation of DNA sequence".

B) Claims 43-57 are objected to because Claim 43 recites, "said fourth", which could be amended to recite, "said fourth primer".

C) Claims 58-62 are objected to because Claim 58 recites, "A kit for in vitro diagnostic method for detecting translocation of DNA sequence", which could be amended to recite, "A kit for **an** in vitro diagnostic method for detecting **a** translocation of DNA sequence".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

New Matter

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 43-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants have not provided support (e.g., by specific page and line numbers) for several limitations of the newly added claims.

1) The recitation of "**indiscriminately** reverse transcribing" RNA extracted from a patient with an anchored primer comprising a "unique" 5' portion and a 3' random portion is not supported by the specification. Specifically, the specification does not support the recitation of "indiscriminately" reverse transcribing; the specification does not support "indiscriminate" amplification, since the method requires a specific primer complementary to the target gene. That is, the specific primer would necessarily amplify a specific target gene, and therefore, this part of the amplification cannot be considered as "indiscriminate".

Applicant argues page 3, lines 19-20, support this amendment. However, this citation is to a prior art reference from which Applicant distinguishes the instant invention. Furthermore, this citation does not include the properties of the primers used for the indiscriminate

amplification (e.g., using a primer comprising a "unique" 5' portion), and therefore, even assuming this citation detailed indiscriminate amplification in general, it does not do so for the primers required by the claimed invention. Accordingly, this argument is not persuasive.

2) The recitation of "second primer being complementary to and binding specifically with cDNA of said target gene", and "third primer being complementary to and binding specifically with a first part of the unique 5' portion of said anchored primer" is not supported by the specification. For example, the recitation of "binding specifically with cDNA of said target gene" and "binding specifically with a first part of the unique 5' portion of said anchored primer" is not present in the specification.

Applicant argues "[t]he description of a "specific DNA primer of the gene *liable to be involved* in a fusion gene" at page 4, lines 8-9 of the specification is believed to support the second primer of claim 43." (See Applicant's response at page 9, emphasis by Examiner). This assertion is not persuasive for several reasons. First, it is not clear as to what is meant by a specific primer of the gene "liable to be involved" in a fusion gene. It is not clear as to what role a specific primer of a gene "liable to be involved" in a fusion gene plays or how this supports the recitation of "said second primer being complementary to and binding specifically with cDNA of said target gene". The cited portion given by Applicant does not specify that the primer is "complementary to and binding specifically with cDNA of said *target* gene". Accordingly, this argument is not persuasive.

With respect to the third primer of Claim 43, Applicant argues "[t]he description of 'a complementary random primer' at page 4, lines 9-10 of the specification, taken in context of the paragraph reference to anchored PCR, will be recognized as a basis for the third primer of claim

43, for example." However, neither this cited portion nor the paragraph reference to anchored PCR (which is not specifically cited by Applicant) provides support for the recitation of "said third primer being complementary to and binding specifically with a first part of the unique 5' portion of said anchored primer". The cited portion suggests that the third primer is a complementary *random* primer, however Claim 43 states, that the third primer is "complementary to and binding specifically with a first part of the unique 5' portion of said anchored primer". Claim 43's limitation that the third primer be "complementary to and binding specifically with" a specific portion of a sequence (e.g., an anchored primer) is not supported by the recitation of a "complementary random primer" as Applicant's argue because a random primer suggests no specific complementarity, which is suggested by the claims. Accordingly, this argument is not persuasive.

3) The recitation of "producing a first collection of amplified products containing a first 5' target gene portion and a first 3' anchor portion" is not supported by the specification.

4) The recitation of "said fourth being complementary to and binding specifically with said target gene at a position 3' to said second primer" is not supported by the specification. Specifically, the recitation of "binding specifically with said target gene at a position 3' to said second primer" is not present in the specification.

Applicant's cite page 5, lines 14-19 for support for the fourth primer. However this section does not support the language present in the claim of "said fourth being complementary to and binding specifically with said target gene at a position 3' to said second primer". Accordingly, this argument is not persuasive.

It is noted that Applicant's urge the Examiner to appreciate that "steps (a)-(c) of Claim 43 generally describe what one of ordinary skill in the art will appreciate as a method of rapid amplification of cDNA ends, or RACE technique, with an 'anchored primer'". (See Applicant's response on page 7). Furthermore, Applicant has attached an excerpt from "PCR PRIMER: A LABORATORY MANUAL", and has described the teachings of said excerpt. (See Applicant's response on pages 8-9). Finally, Applicant's state, "[o]ne of ordinary skill in the art reviewing the present specification, and the references at anchored PCR at page 3, lines 18-24 and page 4, lines 3-11, and elsewhere, of the specification would appreciate as much." (See Applicant's response on page 9).

Applicant's presentation and description of the "PCR PRIMER" reference is appreciated. However, the specification does not describe the specific teachings of this reference. Applicants rely on and cite to page 3, lines 18-24 and page 4, lines 3-11 to proffer support for the teachings of the "PCR PRIMER" reference. However, these pages only describe general amplification methods, and do not describe the specific teachings of the "PCR PRIMER" reference. Accordingly, the description and teachings of the "PCR PRIMER" reference are not considered to be part of Applicant's disclosure, and therefore, does support the newly added claims. It is also noted the specification does not make any mention of the "RACE technique" or "rapid amplification of cDNA ends".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 43-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 43-57 over "indiscriminately" because it is not clear as to how RNA extracted can be reverse transcribed "indiscriminately", when the method requires a specific primer complementary to the target gene (e.g., primer comprising a "unique" 5' portion). That is, the specific primer would necessarily amplify a specific target region, and therefore, this part of the amplification cannot be considered as "indiscriminate".

B) Claims 43-57 over "said reverse transcribing producing patient cDNA" because this recitation lacks antecedent basis because the claim does not previous state "reverse transcribing producing patient cDNA". Furthermore, it is not clear as to what "reverse transcribing producing patient cDNA" encompasses. If Applicant intends to assert that the step of reverse transcribing produces cDNA, it is suggested that Applicant's amend the claim to make this intention clear.

C) Claims 43-62 over "binding specifically with" because it is not clear as to what is encompassed by this recitation. For example, it is not clear if this primer only binds to the specific sequence required by the Claims (e.g., only binds to cDNA of the target gene (second and fourth primers) or a first part of the unique 5' portion of the anchored primer (third and fifth primers)), and no other sequences or it binds with a greater degree of complementarity to these sequences, as compared to other sequences, etc. The specification does not define the recitation of "binding specifically with", and therefore, the metes and bounds of this recitation are unclear.

D) Claims 43-62 over the recitation of "unique" because it is not clear as to what is encompassed or meant by this recitation. It is not clear as to what makes one portion of a

sequence "unique" versus another portion of a sequence that is not considered to be "unique". Furthermore, it is not clear as to whether a "unique" portion could also encompass a random portion. The specification does not define this term, nor does the specification teach one skilled in the art how one differentiates between sequences that are considered to be "unique", and those sequences that are not considered to be unique.

E) Claims 43-52 and 54-57 over "detecting any detectably labeled cDNA" because the claim does not refer to any labels being used in the method or any labeling of cDNA, and therefore, it is not clear as to how one would detect any "detectably labeled cDNA" without the use of labels or of a step of labeling the cDNA.

F) Claims 45 and 51 over "said detectably labeled nucleotides" because this recitation lacks antecedent basis, as the claim(s) from which these claims depend from do not previously refer to labeled nucleotides.

G) Claim 52 over "said solid surface" because this recitation lacks antecedent basis, as the claims from which this claim depends from do not previously refer to a solid surface.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 58 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Morris et al. (USPN 5,770,421).

Given the broadest reasonable interpretation of the claims, the claimed kit comprises

1) A first primer being complementary to and binding specifically with cDNA of said target gene. This encompasses any primer having any degree of complementarity to and which binds or hybridizes to cDNA of a gene.

2) A second primer being complementary to and binding specifically with a first part of a "unique" 5' portion of an anchored primer. This encompasses any primer having any degree of complementarity to and which binds or hybridizes to any 5' portion of any sequence. Absent any definition in the specification with respect to what a "unique" 5' portion is or what is meant by an "anchored primer", the claims have been broadly interpreted as comprising any 5' portion of any sequence.

It is also noted the recitation of "used to reverse transcribe said cDNA from mRNA transcribed from said fusion gene" is considered to be only a statement of purpose and intended result. This claim language does not result in any structural differences between the claimed invention and the product set forth by Morris.

3) At least one probe specific for cDNA encoded by said partner gene, said at least one probe being bound to a solid support. This encompasses a probe bound to a solid support.

It is noted that the specification does not define an "anchored primer", and therefore, a primer capable of hybridizing to another nucleic acid (e.g., a template or target) is considered to be "anchored primer".

Regarding Claim 58, Morris teaches methods of detecting the NPM/ALK fusion gene, including PCR and nucleic acid hybridization (see cols. 2-3, for example). Morris teaches the use of two primers, a first primer being complementary to and binding specifically with cDNA of said target gene and a second primer being complementary to and binding specifically with a first part of a "unique" 5' portion of an anchored primer (see col. 6, 21-23, for example). Morris also teaches probes specific for fusion genes (col. 6 and 17-23, for example), which can be immobilized on solid supports (col. 20, ln. 42-49, for example). Morris also teaches the probe may be labeled with an affinity label, such as biotin (col. 12, ln. 45-49, for example).

Regarding Claim 60, Morris teaches the probes may be immobilized on beads (col. 20, ln. 42-49). It is noted that the claims are drawn to a "miniaturized" support, however, the specification does not define a "miniaturized" support, and therefore, a bead is considered to be a "miniaturized" support.

Finally, Regarding Claims 58 and 60, Morris teaches the above reagents can be packaged in a kit (cols. 4, ln. 9-12 and col. 12).

Applicant's Arguments

First, Applicant argues the specification defines an "anchored primer". Furthermore, Applicant argues the term "anchored primer" was well known to those of ordinary skill in the art and recognized to define a specific species of primers. Applicant also argues "[t]he Examiner's reliance on seemingly general primers as providing the primers of the claimed kits is...inappropriate". (See page 16 of Applicant's response). Finally, Applicant argues the probes of Morris are labeled, whereas the probes of the claimed kit are not labeled.

Response to Applicant's Arguments

Applicant's arguments have been considered, but are not persuasive for the following reasons. First, the specification does not define "anchored primers". Despite Applicant's assertion the specification defines "anchored primer", Applicant has not specified, by page and line number, where the specification defines an "anchored primer", and therefore, this argument is not persuasive. Applicant's assertion that "anchored primers" were well known to those of skill in the art and recognized to define a specific species of primers is also not persuasive for several reasons. First, Applicant has not identified what this specific species of primers, known as "anchored primers" actually comprises. For example, if every primer that is considered to be an "anchored primer" has a specific structure, it is not clear as to what that structure is, nor has Applicant provided the structure. Furthermore, Applicant's have not provided objective evidence to demonstrate that "anchored primers" are well known and comprise a specific structure. In addition, Applicant's assertion that any reliance on "general" primers for teaching the primers of the claimed invention is inappropriate is not persuasive because this appears to be an opinion that is not supported by the record or by objective evidence. Finally, the claims are drawn to kits "comprising" at least one probe, and therefore, the kit can comprise at least one probe and any other elements, such as a label. Thus, any prior art that comprises a kit comprising a labeled probe would still be encompassed by the claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 43-48 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (USPN 5,547,838), in view of Holtke et al. (Cellular and Molecular Biology (1995) 41(7), 883-905, previously cited).

Regarding Claim 43, Nisson teaches an in vitro diagnostic method for detecting translocation of DNA sequences (t(8;21)) involved in cancer (acute myelogenous leukemia (AML)), said translocation forming at least one rearranged fusion gene, said at least one rearranged fusion gene comprising a target gene and a partner gene, said method comprising the steps of:

a) indiscriminately reverse transcribing RNA extracted from a patient sample with a first primer, said first primer being a random anchored primer, said reverse transcribing producing patient cDNA, said anchored primer comprising a unique 5' portion and a 3' random portion (col. 5, lines 25-41, but see also col. 9, lines 20-26, for example);

b) amplifying all of the patient cDNA with a first pair of primers, said first pair of primers comprising a second primer and a third primer, said second primer being complementary to and binding specifically with cDNA of said target gene and said third

primer being complementary to and binding specifically with a first part of the unique 5' portion of said anchored primer, said amplifying all of the patient cDNA producing a first collection of amplified products containing a first 5' target gene portion and a first 3' anchor portion (col. 5, lines 45-50, but see also col. 9, lines 26-33, for example);

c) amplifying said collection of amplified products with a second pair of primers in a nested amplification reaction, said second set of primers comprising a fourth primer and a fifth primer, said fourth being complementary to and binding specifically with said target gene at a position 3' to said second primer, said fifth primer containing a sequence which binds to at least a portion of said first pad of the unique 5' portion of said anchored primer, said amplifying said collection producing a second collection of amplified products containing a second 5' target gene portion and a second 3' anchor portion, said second collection of amplified products further comprising detectably labeled nucleotides incorporated in to said products during amplification (see col. 5, line 66 to col. 6, line 23, for example);

d) contacting said second collection of amplified products with at least one nucleic acid probe or at least one plurality of nucleic acid probes, wherein said at least one nucleic acid probe or each of said plurality of nucleic acid probes is specific for a partner gene, under conditions wherein any cDNA corresponding to said partner gene of the fusion gene present in said collection will hybridize with said probe (see col. 6, lines 40-53, and col. 7, lines 6-13, for example).

Nisson does not teach detecting any detectably labeled cDNA from said second collection of amplified products bound to said probe as an indication of translocation of DNA sequences.

That is, while Nisson teaches the detection of the translocation by using labeled probes, Nisson does not teach that a label is incorporated into the amplification product.

However, detecting amplification products by incorporating labels into the amplification product has been found to be advantageous in the prior art. Specifically, Holtke teaches incorporating DIG-dUTP into a PCR product using the DIG (digoxygenine) system (see page 884, column 1; pages 886-887, 889-890, 897 and 889). Holtke teaches the DIG-labeled PCR products can be detected on membranes, with the PCR ELISA plate, or can be analyzed by streptavidin-coated microtiter plates (see page 888, for example). More specifically, Holtke teaches the use of the DIG labeling system can be used in RT-PCR assays (see page 887, for example). Holtke teaches the digoxygenine labeling and detection system is advantageous because "this label does not occur naturally, high-affinity antibodies were readily available from development of diagnostic and therapeutic reagents, the label is chemically, well accessible, it can be derivatized, and coupled to linkers and to nucleotides, its size and hydrophilicity enables the incorporation of hapten labeled nucleotides into nucleic acid probes by DNA and RNA polymerases" (see page 884). Holtke also teaches the DIG system "enables further applications due to the possibility to bind labeled nucleic acids specifically to solid phases, e.g., microtiterplates and magnetic beads", and concludes that the DIG system is one of "the most successful labeling and detection systems", since it is "proven to have advantages regarding both sensitivity and specificity" (see pages 884 and 903). Accordingly, Holtke teaches the advantages of incorporating DIG-UTP into a PCR product for an advantageous detection of nucleic acids.

Accordingly, in view of the teachings of Holtke, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of

Nisson so as to have included the steps of using the digoxygenine labeling and detection system, and therefore, have incorporated a label into the PCR product for subsequent detection of a translocation. One of ordinary skill in the art would have been motivated to have used the DIG labeling and detection system of Holtke, because "this label that does not occur naturally, high-affinity antibodies were readily available from development of diagnostic and therapeutic reagents, the label is chemically, well accessible, it can be derivatized, and coupled to linkers and to nucleotides, its size and hydrophilicity enables the incorporation of hapten labeled nucleotides into nucleic acid probes by DNA and RNA polymerases" (see page 884). Furthermore, the skilled artisan would have been motivated to use the DIG labeling and detection system because Holtke teaches the DIG system "enables further applications due to the possibility to bind labeled nucleic acids specifically to solid phases, e.g., microtiterplates and magnetic beads", and concludes that the DIG system is one of "the most successful labeling and detection systems", since it is "proven to have advantages regarding both sensitivity and specificity" (see pages 884 and 903).

Regarding Claim 44, Nisson teaches any one of the first primer, the second primer, the third primer, the fourth primer and the fifth primer is 25 to 40 nucleotides in length (see cols. 7 and 9, for example).

Regarding Claim 45, Holtke teaches DIG-labeled nucleotides (e.g., DIG-dUTP) (see page 884, for example).

Regarding Claims 46-47, Holtke teaches DIG-labeled PCR products can be detected by covalently bound probes via an ELISA plate (see page 888, for example).

Regarding Claim 48, Nisson teaches said first primer consists of a sequence containing a cassette of 40 to 60 nucleotides, wherein said 3' random portion comprises a sequence of 10 to 20 (dT)s (see col. 9, lines 20-24, for example).

Regarding Claim 57, Nisson teaches identifying said partner gene of the fusion gene from binding of said probes (see cols. 6-7, for example).

12. Claims 49-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (USPN 5,547,838), in view of Holtke et al. (Cellular and Molecular Biology (1995) 41(7), 883-905, previously cited), as applied to Claims 43-48 and 57 above, and in further view of Felix et al. (USPN 6,368,791, previously cited).

The teachings of Nisson and Holtke are presented above and are incorporated herein. Specifically, Nisson and Holtke teach an in vitro diagnostic method for detecting translocation of DNA sequences (t(8;21)) involved in cancer (acute myelogenous leukemia (AML)), said translocation forming at least one rearranged fusion gene, said at least one rearranged fusion gene comprising a target gene and a partner gene, wherein the method comprises a RACE-based PCR screening assay. While Nisson and Holtke teach improved methods for diagnosing the presence or onset of AML by analyzing the t(8;21) translocation, they do not teach the method wherein the target gene is MLL.

However, Felix et al. teaches translocations in the MLL gene at chromosome band 11q23 "is associated with most cases of ALL which occur during infancy and with most monoblastic variants of AML which occur during the first four years of life" (col. 1, lines 46-51, see also cols. 14 and 15). That is, rearrangements of MLL are known to be associated with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) is children. Feliz also

teaches that PCR can be used for identifying MLL gene rearrangements (see cols. 3-8, 13-16, 21-22 and Examples 1-7).

Accordingly, in view of the teachings of Felix, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nisson and Holtke so as to have detected rearrangements in the MLL gene, in order to have achieved the benefit of detecting AML in young children. Nisson and Holtke teach improved methods for detecting AML using the t(8;21) translocation, however, one of ordinary skill in the art would have been motivated to use the method of Nisson and Holtke, as applied to the MLL gene (as the target gene), since rearrangements of the MLL are also associated with AML. Therefore, one of ordinary skill in the art would have been motivated to have used the method of Nisson and Holtke for detecting rearrangements in the MLL gene, in order to have detected leukemia in children, such as ALL and AML.

Regarding Claim 50, Felix teaches probes specific for known MLL fusion partner genes (see cols. 28, 30, 31, 37 and 38, for example).

Regarding Claim 51, Holtke teaches DIG-labeled nucleotides (e.g., DIG-dUTP) (see page 884, for example).

Regarding Claim 52, Holtke teaches DIG-labeled PCR products can be detected by covalently bound probes via an ELISA plate (see page 888, for example).

Regarding Claim 53, Holtke teaches the method of claim 52 wherein said marker is digoxygenine, said detecting comprises contacting said marker with anti-digoxygenine antibodies coupled to an enzyme, said enzyme being capable of reacting with a substrate of said enzyme to release a detectable product (see page 884, for example).

Regarding Claim 54, Felix teaches the cancer is leukemia (see col. 1, for example).

13. Claims 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (USPN 5,547,838), in view of Holtke et al. (Cellular and Molecular Biology (1995) 41(7), 883-905, previously cited), in view of Felix et al. (USPN 6,368,791, previously cited), as applied to Claims 49-54 above, and in further view of Kaneko et al. (Genes, Chromosomes & Cancer (March, 1997) 18: 228-231).

The teachings of Nisson, Holtke and Felix are presented above and are incorporated herein. Specifically, the references teach an in vitro diagnostic method for detecting translocation of DNA sequences involved in cancer (e.g., leukemia), said translocation forming at least one rearranged fusion gene, said at least one rearranged fusion gene comprising a target gene and a partner gene, wherein the method comprises a RACE-based PCR screening assay. The references do not teach the cancer is a solid tumor, such as Ewing tumor.

However, Kaneko teaches Ewing sarcoma (tumor), which is associated with cancer in children, is caused by a chromosomal translocation that is similar to that of the MLL (see abstract and pages 229 and 231). Specifically, Kaneko teaches that Ewing sarcoma is caused by an inversion/insertion, which is consistent with the MLL-AF10 fusion (see page 229, 2nd column).

Accordingly, in view of the teachings of Kaneko, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nisson, Holtke and Felix to have detected translocations in Ewing sarcoma. One of ordinary skill in the art would have been motivated to have used the method of Nisson, Holtke and Felix for detecting Ewing sarcoma because like rearrangements in MLL and the t(8;21) translocation,

Ewing sarcoma results in cancer among children, and furthermore, Kaneko expressly teaches that MLL and Ewing translocations have similar mechanism, and therefore it would have been obvious to detect these translocations when diagnosing a child suspected of having leukemia.

14. Claims 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (USPN 5,547,838), in view of Holtke et al. (Cellular and Molecular Biology (1995) 41(7), 883-905, previously cited), as applied to Claims 43-48 and 57 above, and in further view of the Stratagene Catalog (1988), previously cited.

The teachings of Nisson and Holtke are presented above and are incorporated herein. The references teach the reagents of the claimed kit (see above). Nisson also suggests packaging the reagents of his method into a kit (see col. 8, for example). Furthermore, Holtke teaches the DNA chip, wherein at least one probe is bound to the chip through a biotin group bonding to streptavidin coupled to said support (see page 899, for example). However, the references do not teach packaging all of the reagents of Nisson and Holtke into a kit.

However, reagent kits for performing DNA assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the above reagents in a kit for the expected benefits of convenience and cost-effectiveness for practitioners of the art.

15. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nisson et al. (USPN 5,547,838), in view of Holtke et al. (Cellular and Molecular Biology (1995) 41(7), 883-

905, previously cited), in view of Felix et al. (USPN 6,368,791, previously cited), as applied to Claims 49-54, and in further view of the Stratagene Catalog (1988), previously cited.

The teachings of Nisson, Holtke and Felix are presented above and are incorporated herein. The references teach the reagents for an in vitro diagnostic method for detecting translocations of DNA sequences involved in cancer (e.g., MLL as a target gene). However, the references do not teach packaging all of the reagents into a kit.

However, reagent kits for performing DNA assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the above reagents in a kit for the expected benefits of convenience and cost-effectiveness for practitioners of the art.

16. Claims 59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al. (USPN 5,770,421), as applied to claims 58 and 60 above, in view of Holtke et al. (Cellular and Molecular Biology (1995) 41(7), 883-905, previously cited), and in further view of the Stratagene Catalog (1988), previously cited.

The teachings of Morris are presented above and are incorporated herein. Specifically, Morris teaches a kit comprising two primers of the claimed kit and a probe immobilized to a solid support and methods of detecting the NPM/ALK fusion gene, including PCR and nucleic acid hybridization. Morris also teaches that the probe can be labeled with an affinity label, such

as biotin. Morris does not teach the probe bound to a solid support through a biotin group bonded to streptavidin coupled to said support or the use of a DNA chip as a solid support.

The teachings of Holtke et al. are presented above. Specifically, Holtke teaches the advantages of the DIG labeling and detection system in the detection of nucleic acids (see above). Hotlke teaches the DIG system can be used in conjunction with many types of nucleic acid methods, such as those used by Morris (e.g., PCR) (see page 887, for example). Furthermore, Holtke teaches the DIG system can encompass the use of a DNA chip, wherein at least one probe is bound to the chip through a biotin group bonding to streptavidin coupled to said support (see page 899, for example) teaches the rapid detection of nucleic acids using an array of probes (see abstract and col. 2, for example).

Accordingly, in view of the teachings of Holtke, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Morris to have included the probe bound to a solid support through a biotin group bonded to streptavidin coupled to said support, wherein said support could be a DNA chip, in order to have achieved the benefits stated above of the DIG labeling and detection system for improved detection nucleic acids.

The references do not teach packing all of the reagents of Morris and Holtke in a kit.

However, reagent kits for performing DNA assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time

the invention was made to have packaged the above reagents in a kit for the expected benefits of convenience and cost-effectiveness for practitioners of the art.

Conclusion

17. No Claims are allowable.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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June 3, 2004

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